# The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication

Dicapite, Suzanne; Upthegrove, Rachel; Mallikarjun, Pavan

*DOI:*
10.1111/eip.12385



*Document Version*
Peer reviewed version

*Citation for published version (Harvard):*
Dicapite, S, Upthegrove, R & Mallikarjun, P 2018, 'The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication', *Early Intervention in Psychiatry*, vol. 12, no. 5, pp. 893-899. https://doi.org/10.1111/eip.12385


# The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication


| | |
|---|---|
| Journal: | *Early Intervention in Psychiatry* |
| Manuscript ID | EIP-2016-061.R1 |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | 12-Jul-2016 |
| Complete List of Authors: | Di Capite, Suzanne; University of Birmingham, Department of Psychiatry<br>Upthegrove, Rachel; University of Birmingham, Institute of Clinical Sciences ; Forward Thinking Birmingham, Early Intervention Service<br>Mallikarjun, Pavan; University of Birmingham, Institute of Clinical Sciences / School of Psychology; Forward Thinking Birmingham, Early Intervention Service |
| Keywords: | Antipsychotics, first episode psychosis, Discontinuation, relapse rates, risk factors |
| | |

# The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication

Suzanne Di Capite[1], Rachel Upthegrove[1,2], Pavan Mallikarjun[1, 2,3*]

1. Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham
2. Birmingham and Solihull Mental Health Foundation Trust
3. School of Psychology, College of Life and Environmental Sciences, University of Birmingham

*Correspondence
Pavan Mallikarjun
p.mallikarjun@bham.ac.uk.
The Barberry, University of Birmingham, 25 Vincent Drive Edgbaston Birmingham B152FG.
Phone: 01213012355

**Acknowledgements**
The authors would like to thank Dr Sayeed Haque for his statistical advice and to the Birmingham Early Intervention teams: North, East, South and West.

**Contributors:**

PM had the original idea for the study. SDC, PM and RU designed the protocol. SDC conducted the data collection and the statistical analysis, and wrote the first draft. All authors undertook quality assessment and approved the final manuscript.

## Abstract

**Aims:** To determine the "real world" relapse rate in patients with first-episode psychosis who had discontinued antipsychotic medication and identify socio-demographic and clinical factors associated with the risk of relapse. **Methods:** Quantitative data were obtained via case-note review on 63 patients with first-episode psychosis who had discontinued antipsychotic medication from Birmingham Early Intervention Service between 2012 and 2015. The follow-up period was until either: an occurrence of a relapse; end of 12 month study period; end of patient's case-note record. Relapse was defined as a return of symptoms requiring: home treatment, hospital admission or was based on clinical teams' decision as having a relapse. A pro-forma targeted pre-defined socio-demographic and clinical factors. Survival analysis was undertaken to estimate the 12 month relapse rate following discontinuation of antipsychotics and Cox regression performed to identify relapse predictors. **Results:** The Kaplan-Meier 12 month relapse estimate was 67% (95% confidence interval, 54%, 80%). Significant factors ($P$ <0.05) independently associated with an increased risk of relapse following discontinuation of antipsychotic medication were: male gender, not being in education, employment or training (NEET) and number of previous psychiatric hospital admissions. **Conclusions:** Relapse is common after discontinuation of antipsychotic medication following recovery from a first-episode psychosis. It is important patients who wish to discontinue their medication are informed of the high relapse rates and the associated risks.

Furthermore, male patients, patients with NEET status and those who have had previous hospital admissions may require closer monitoring.

**Keywords:** antipsychotics, discontinuation, first-episode psychosis, relapse, risk factors.

## Introduction

Preventing relapse is one of the most important clinical targets in the management of first-episode psychosis (FEP); approximately 80% of patients treated following FEP, relapse within the first five years. [1,2] Relapse compromises the outcome of psychotic disorders, with each new episode significantly increasing the development of treatment resistant symptoms.

It has been well established that maintenance medication plays an important role in reducing the risk of relapse among FEP patients.[3] However, the optimum duration of maintenance medication is yet to be determined and published guidelines are not united in their recommendations. A recent systematic review of 14 guidelines for maintenance treatment after a first-episode of schizophrenia found that six were not opposed to discontinuing antipsychotics after one to two years, while two discouraged discontinuation[4]. In the remaining six guidelines, medication discontinuation was not mentioned.[4]

The question of how long to continue antipsychotic treatment after FEP is common among patients, and clinicians face difficulties convincing patients that indefinite treatment may be indicated. Premature discontinuation of medication is common among patients; a randomised controlled trial comparing atypical

antipsychotics in FEP patients reported 70% of patients discontinued before the end of the 12 month study period.[5]

Given the high rates of discontinuation reported, clinical interest in the relationship between relapse risk and discontinuation of medication in patients with FEP has grown. Controlled trials of treatment discontinuation consistently report higher relapse rates compared to maintenance treatment. However, studies to date have yielded a range of relapse rates (between 41% and 80%) following 12 months discontinuation.[3,6-8] A systematic review estimated a weighted mean one-year relapse rate of 77% in six controlled trials.[9] However the generalisability of these studies may be limited as patients required capacity to consent for inclusion, and, as volunteers, reflected a research population. Therefore, discontinuation relapse rates from a "real world" setting (i.e. representing clinical practice) may differ considerably.

In addition to the clinical importance of estimating relapse rates representative of all patients who discontinue antipsychotic medication, it is also essential to be able to predict relapse risk. To date, medication non-adherence has been the only factor to robustly predict relapse in FEP patients, and is associated with a four-fold increase in relapse risk.[10] The other risk factors associated with relapse include persistent substance use disorder, carers' critical comments and poor premorbid adjustment[10]. Demographic and clinical variables such as younger age at first onset psychosis[11], duration of untreated psychosis[12] and male gender[13,14] have been reported by some naturalistic studies to predict relapse, although these have failed to be replicated in later studies.[2,15-17] It has been proposed that there may be relapse predictors specific to patients who

discontinue medication.[3] It is imperative to be able to accurately predict relapse in these patients in order to allow identification of those at higher risk.

Thus, this study has two main objectives: first, to determine the "real world" relapse rate in patients with FEP who had discontinued antipsychotic medication, and second, to identify the socio-demographic and clinical factors associated with the risk of relapse.

## Method

### Study setting and population

The study population was drawn from patients under the care of the Birmingham Early Intervention Service (EIS) between 2012 and 2015. The EIS is responsible for the treatment of young people aged 16 - 35 with FEP. With a total caseload of approximately 700 patients, the service comprises five teams spanning the Birmingham and Solihull Mental Health Trust (BSMHFT); an area of diverse ethnic and socio-demographic communities.

Patients were included on meeting the following criteria:

- discontinued antipsychotic medication for any reason
- had a clinical diagnosis of FEP conforming to ICD-10 codes F20-29, F30.2, F31.2, F31.5, F32.3 and F33.3[18] (due to the diagnostic uncertainty during the early stages of psychosis, a broad diagnostic range was chosen)
- experienced a significant reduction of symptoms as judged by the clinical team prior to discontinuing medication (i.e. had recovered)

Patients were excluded if they had i) discontinued antipsychotic medication for less than four weeks, or ii) less than four weeks antipsychotic treatment prior to discontinuation, (as these time periods were considered too short to be defined as discontinuation or as an effective treatment episode). Patients with insufficient case notes were also excluded.

**Study design**

Quantitative data were obtained from retrospective electronic case-note review. Case records were analysed from the point medication was discontinued. The follow-up period was until: an occurrence of a relapse; the end of the 12 month study period; or the end of the patient's case record if less than 12 month's follow-up data (as this could be accounted for by statistical analysis). All data were extracted by the author and were based on routine assessment by clinicians as documented in BSMHFT electronic patient records.

**Procedure**

The study protocol was disseminated to all clinical teams within the Birmingham EIS. Clinical teams identified patients who had discontinued medication between 2012 and 2015. Case notes of eligible patients were subsequently screened by the author using the eligibility criteria to determine the final sample.

**Ethical approval**

The study protocol was approved by BSMHFT Research and Innovation department and by the BMedSc Population Sciences and Humanities Internal Ethics Review Committee (IERC). In accordance with National Research Ethics Service (NRES) guidelines for a study involving previously collected routine

clinical data, specific consent procedures were not required [19] and thus the sample consisted of all patients who met the eligibility criteria.

## Outcome measures

### Relapse

Relapse was defined as a return of symptoms requiring one of the following: home treatment, an informal mental health admission to hospital, a compulsory admission under the Mental Health Act (2007)[20], or was based on the clinician's judgement of having a relapse. This definition is representative of the BSMHFT EIS procedure to detect a relapse of symptoms. Relapse evaluated was the first relapse following the patient's FEP. The relapse status, definition and time to relapse were recorded.

### Predictor variables

A standard pro-forma targeted pre-defined socio-demographic and clinical factors, and was developed from a systematic review that explored factors associated with relapse in FEP.[10] Socio-demographic variables were evaluated upon study entry and included: age, gender, ethnicity, marital status, education level, accommodation, employment status and smoking status. Accommodation status was categorised into settled versus not settled; not settled was defined as being in supported housing or temporary accommodation.

Clinical variables were: clinical diagnosis, psychiatric co-morbidities, psychiatric family history, number of previous psychiatric hospital admissions, substance misuse, age at onset of psychosis, duration of untreated psychosis (DUP), duration of untreated illness (DUI), duration of antipsychotic treatment prior to discontinuation and type of antipsychotic medication (oral or depot). Due to the sample only including FEP patients, previous psychiatric hospital

admissions were evaluated prior to the patient's FEP. DUP was defined as the period (in days) between first appearance of psychotic symptoms and the onset of criterion treatment (defined as antipsychotic treatment for more than two weeks). DUI was defined as the interval (in days) between the onset of non-specific symptoms and the onset of criterion treatment. Both DUP and DUI data were based on routine standardised clinical interview as recorded in case notes.

**Statistical analysis**

A survival analysis was used to estimate the cumulative rate of relapse, with censoring of data to account for differentiated duration of follow-up of study subjects. Data were censored if no relapse occurred during follow-up.

Cox proportional hazards regression was used to identify predictors of relapse by examining time to relapse and its relationship with independent variables. Proportional hazard assumption was assessed graphically using log minus log survival plots. Univariate Cox proportional hazards regression analysis was first performed on each potential predictor. Variables with $P \leq 0.1$ were entered into a multivariate Cox proportional hazards model. A forward stepwise likelihood ratio for variable selection was used in the multivariate model, with $P < 0.05$ as the entering criterion. Missing values were excluded from the analysis. A similar analysis was conducted in patients who did not relapse despite stopping medication to identify factors associated with non-relapse.

## Results

A total of 133 patients were identified by the clinical teams' to have discontinued antipsychotics. Following assessment of eligibility, 70 (52.6%) were excluded

from the study for the following reasons: insufficient case notes (n = 29, 41.4%); not meeting inclusion criteria (N=21, 30%) and discontinuation period of less than four weeks (n = 20). For those excluded for not meeting the inclusion criteria (n=21, 30%), 18 were due to partial non-concordance (i.e. not fully discontinued medication) and the remaining 3 due to a reduction in symptoms being deemed insignificant (as judged by the clinical team). Thus, data were collected for 63 patients.

**Sample characteristics**

Table 1 summarises the socio-demographic and clinical characteristics of the sample.

The sample was 73% male and the median age at discontinuation was 22 years (IQR = 6). The largest ethnic group was Asian (n = 22, 35.0%), followed by White (n = 17, 27.0%) and Black (n = 13, 20.6%). Two-thirds of the sample were classified as not being in education, employment or training (NEET) (n = 42, 66.7%). The most common diagnosis categories were psychosis not otherwise specified (NOS) (n = 24, 38.1%) and schizophrenia (n = 21, 33.3%). Prior to discontinuation, the median duration of antipsychotic treatment was 8.5 months (IQR = 11.3; range 1-36), of which oral medication was the most common type (n = 53, 84.1%). The median duration of follow up was 6 months (IQR = 6 months).

**Relapse**

Out of the 63 patients, 36 relapsed (57%) by the end of the 12 months; of those that relapsed, the majority resulted in either an informal or compulsory hospital admission (n = 19, 52.8%), with a greater proportion of compulsory admissions

(n = 11, 30.6%). Taking into account censoring, the Kaplan-Meier estimate of the proportion relapsed at, or earlier than 12 months was 67% (95% confidence interval (CI), 54%, 80%) (Figure 2). The median time to relapse was 8 months (95% CI, 6.03, 9.97).

Given the differentiated length of antipsychotic treatment prior to discontinuation, patients were grouped into: ≤12 months antipsychotic treatment (n = 42, 66.7%) and >12 months treatment (n = 20, 31.7%). No significant differences were found in time to relapse in these two groups. ($X^2$ = 0.001, d.f. = 1, *P* = 0.978).

**Predictors of relapse**

Several of the socio-demographic and clinical variables explored were found to be statistically insignificant (*P* >0.05) in the univariate analysis, and were: age at discontinuation, marital status, education level, accommodation, diagnosis, age at onset of FEP, DUP, DUI, psychiatric co-morbidities, psychiatric family history, duration of antipsychotic treatment and type of antipsychotic medication.

Results of the relapse predictors in the univariate Cox model analysis with *P* ≤0.1 are shown in Table 2. Significant univariate predictors included male gender, NEET, number of previous psychiatric hospital admissions and substance misuse. Three independent predictors for relapse were identified from the multivariate Cox model analysis (Table 2). Patients who were male had a 3.7 times higher risk of relapse (Exp B = 3.72; 95% CI, 1.42, 9.78; *P* = 0.008). NEET status was associated with a two-fold increase in relapse risk when compared to being in education, training or employment (Exp B = 2.24; 95% CI, 1.01, 4.97; *P* = 0.047). The number of previous psychiatric hospital

admissions was identified as a highly significant clinical predictor, with the risk of relapse increasing by approximately two times with every one unit increase in previous hospital admission (Exp B = 1.94; 95% CI, 1.31, 2.88; *P* = 0.001). None of the identified risk factors were found to be statistically significant in predicting non-relapse in this sample of patients with first episode psychosis who had stopped their medication.

## Discussion

This study sought to address the "real world" relapse rate and to identify which factors (socio-demographic and clinical) were associated with relapse in a sample of FEP patients, who had discontinued antipsychotic medication. Approximately two-thirds of the sample relapsed within 12 months following discontinuation of antipsychotics, with male gender, NEET and increasing number of previous psychiatric hospitalisations being independently associated with a higher risk of relapse.

### Relapse

This study's relapse rate of 67% is in keeping with the literature, reporting between 41% and 80% of FEP patients who discontinue medication go on to relapse within the first year.[3,7-9] The higher relapse rates reported (approximately 80%[7-9]) may be explained by the use of symptom-based definitions and the intensive follow up and monitoring that existed, allowing detection of relapses earlier. The relapse criterion for this study was less stringent, which was reflected by the high hospitalisation rate (52%) among those that relapsed, in comparison to previous studies.[6-8] Nevertheless, it was based on the normal stepwise procedure used by the EIS to detect a relapse,

therefore likely to be better representative of “real world” clinical practice. Additionally, previous research conducted by Chen *et al*.[8] estimated a more pragmatic relapse rate (69%) based on information from case notes, including only relapses deemed clinically significant, which is comparable to the relapse estimated in this study.

The high hospitalisation rate among those who relapsed demonstrated that this study captured clinically significant relapses. This highlights the need for closer follow-up of patients once they are known to discontinue medication in order to identify relapses earlier before pronounced deterioration occurs. It would be useful for future studies to not only quantify relapse rates but also evaluate the clinical impact of the relapses.

An important finding was that relapse was not found to be related to the duration of previous antipsychotic medication (which ranged from 1 month to 36 months; median treatment duration being 8.5 months). This is concurrent with research by Chen *et al*.[8] Furthermore, from previous discontinuation trials, there is no apparent indication of reduced relapse risk with longer treatment periods. Discontinuation after 3, 12 and 24 months in three separate trials all reported 12 month relapse rates of around 80%.[7,8,21] This has implications for clinical practice, and suggests that lengthening treatment after a FEP does not reduce the relapse risk. However, the optimum point in time at which medication can safely be discontinued has yet to be established.

**Predictors of relapse**

The strongest predictor was male gender, which was associated with approximately a four-fold increase in risk of relapse. Previous studies have

been mixed with regards to the relationship between gender and relapse, with some suggesting an association[13,14] while others have failed to show any association.[3,12] Nonetheless, generally in FEP patients, gender effects have been reported with regards to functional outcome; male patients have been shown to have poorer functional outcome after a first-episode, suggesting males may have an increased vulnerability to relapse.[13] Noteworthy, male gender has been reported to be a predictor of medication discontinuation[22] and so the high proportion of males in this sample may have enhanced the apparent difference in relapse risk. Nevertheless, this higher proportion of males to females is compatible with the gender split seen in this EIS.[23]

NEET was associated with an approximately two times increase risk in relapse compared to those in employment, education or training. This finding ties in with a FEP follow-up study reporting early vocational recovery to be associated with longer term recovery.[24] Early vocational recovery is considered a key component of recovery and it has been observed that those who only have one episode and recover fully are less likely to be NEET.[24] NEET could be used as a broad measure of poor functional outcome and suggests the importance of interventions facilitating vocational recovery.

The association between previous number of psychiatric hospital admissions and increased relapse risk is concurrent with studies examining predictors of hospital readmission in schizophrenia.[25,26] It has been shown that a history of hospitalisation is associated with a higher chance of earlier rehospitalisation in patients with schizophrenia.[27] Although in this study previous psychiatric admissions related to admissions prior to the patients' FEP diagnosis,

hospitalisation typically indicates a higher level of symptom severity experienced by patients. Therefore, it could suggest patients with previous psychiatric admissions (prior to FEP) go onto have a more unstable illness.

**Strengths and limitations**

The diverse ethnic sample, the inclusion of all-cause discontinuation and patients not limited to those with motivation and capacity to consent allowed an estimate of relapse which is perhaps more generalisable to typical clinical practice.

However, these findings must be interpreted in light of a number of limitations. The method used to determine the sample likely introduced recall and selection biases. The method involved clinicians identifying patients who had discontinued medication; clinicians are more likely to recall those patients who had previously discontinued medication which resulted in a relapse, likely inflating the relapse estimate. Furthermore, patients who discontinued medication covertly and those who had successfully discontinued may have been less likely to have been identified. These biases perhaps could have been reduced through screening a random selection of patients, stratified by demographic and clinical factors, within the EIS using the eligibility criteria. Plasma antipsychotic levels monitoring would be the ideal way to establish adherence to medication, which was not available in this study due to the design constraints.

The reliability of the relapse and predictor estimates were further limited by the small sample size. The sample size may have been insufficient to detect weaker predictors and was also restricted by the quality of the case notes: a

high proportion of the potentially eligible sample were excluded due to insufficient case notes (41%) and it is possible a proportion of these might have successfully fulfilled the eligibility criteria.

It is important to note that for inclusion, patients were judged as having significant reduction in symptoms before discontinuation; however, the time period for the recovery was not specified, which could have been a factor associated with relapse. Other potentially important relapse factors were not captured, such as level of insight and past adherence. Larger sample sizes and prospective longitudinal studies are required to be able account for these limitations.

**Conclusion**

Relapse is common in “real world” clinical practice following discontinuation of antipsychotic medication following recovery from a FEP. It is important for clinicians to inform patients who wish to discontinued their medication of the high relapse rates, and should ensure closer monitoring of patients who discontinue medication. Patients who are male, NEET status and have a history of psychiatric admissions should be recognised by health care professionals as having an increased risk of relapse, and suggests continued medication in these patients. However, these findings need to be replicated in larger independent samples. It may also be useful for future work to identify those patients who can discontinue medication without risk of relapse through investigating factors that may be protective. This will further aid clinicians’ decision-making when confronted with patients requesting discontinuation.

## References

1. Wiersma D, Nienhius FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: A 15-year followup of a dutch incidence cohort. *Schizophr Bull*. 1998; 24(1): 75-85.

2. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; 56(3): 241-247.

3. Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J. Fluphenazine vs placebo in patients with remitted, acute first episode schizophrenia. *Arch Gen Psychiatry* 1982; 39(1): 70.

4. Takeuchi H, Suzuki T, Uchida H, Watanabe K, Mimura M. Antipsychotic treatment for schizophrenia in the maintenance phase: A systematic review of the guidelines and algorithms. *Schizophr Res* 2012 ; 134(2-3): 219-225.

5. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: A randomized, double-blind 52-week comparison. *Am J Psychiatry* 2007; 164(7): 1050-1060.

6. Gaebel W, Riesbeck M, Wolwer W, Klimke A, Eickhoff M, Von WM. Relapse prevention in first episode schizophrenia-maintenance vs intermittent drug treatment with prodrome-based early intervention: Results of a randomised controlled trial within the german research network on schizophrenia. *J Clin Psychiatry* 2011; 72: 205.

7. Gitlin M, Nuechterlein K, Subotnik KL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent- onset schizophrenia. *Am J Psychiatry* 2001; 158(11): 1835-1842.

8. Chen EYH, Hui CLM, Lam MML, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: Randomised controlled trial. *BMJ* 2010; 341: c4024

9. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: A systematic review. *Schizophr Res* 2014; 152(2-3): 408-414.

10. Alvarez-Jimenez M, Hetrick A, Bendall SE, et al. Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Schizophr Res* 2012; 139(1-3): 116-128.

11. Haro JM, Eaton WW, Bilker WB. Predictability of rehospitalisation for schizophrenia. *Eur Arch Psych and Cl Neuro*. 2006b; 244:241.

12. Johnstone EC, Crow TJ, Johnson AL, MacMillan JF. The northwick park study of first episodes of schizophrenia. I. presentation of the illness and problems relating to admission. *Br J Psychiatry* 1986;148:115-120.

13. Angermeyer MC, Goldstein JM, Kuehn L. Gender differences in schizophrenia: Rehospitalization and community survival. *Psychol Med* 1989; 19(2): 365-382.

14. Tohen M, Stoll AL, Strakowski SM. The Mclean first-episode psychosis project: Six month recovery and recurrence outcome. *Schizophr Bull* 1992; 18(2): 273-82

15. Johnstone EC, MacMillan JF, Frith CD. Further investigation of the predictors of outcome following first schizophrenia episodes. *Br J Psychiatry* 1990; 157: 182-89.

16. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophr Res* 2005; 77(1): 99-104.

17. Lenior ME, Dingemans PMAJ, Schene AH. Predictors of the early 5 year course of schizophrenia: A path analysis. *Schizophr Bull* 2005; 31: 781-91.

18. World Health Organisation. *The ICD-10 international classification of diseases and related health problems.* Tenth Revision ed. Geneva: WHO; 1992.

19. NHS health research authority ethical approval requirements. http://www.nres.nhs.uk/applications. Accessed 12/10, 2014.

20. The mental health act 2007. http://www.legislation.gov.uk/ukpga/2007. Accessed 05/1, 2015.

21. Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: A 3-year open-label clinical study. *J Clin Psychiatry* 2012; 73(4): e541-7.

**Table 1. Sample characteristics (N=63)**

22. Kampman O, Laippala P, Vaananen J, et al. Indicators of medication compliance in first-episode psychosis. *Psychiatry Res* 2002; 110(1): 39-48.

23. Kam.S.M., Singh SP, Upthegrove R. What needs to follow early intervention? predictors of relapse and functional recovery following first episode psychosis. *Early Interv Psychiatry* 2015: 9(4): 279-83

24. Alvarez-Jimenez M, Gleeson JF, Henry LP, et al. Road to full recovery: Longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychol Med* 2012; 42(3): 595-606.

25. Mortensen PB, Eaton WW. Predictors for readmission risk in schizophrenia. *Psychol Med* 1994; 24(1): 223-232.

26. Swett C. Symptom severity and number of previous psychiatric admissions as predictors of readmission. *Psychiatr Serv* 1995; 46(5): 482-485.

27. Olfson M, Mechanic D, Boyer CA, Hansell S, Walkup J, Weiden PJ. Assessing clinical predictions of early rehospitalization in schizophrenia. *J Nerv Ment Dis*. 1999; 187(12): 721-729.

| Socio-demographic variables | | N (%) or Median (IQR) |
|---|---|---|
| Gender | Male | 46 (73.0) |
| | Female | 17 (27.0) |
| Age (years) | | 22 (6) |
| Ethnicity | White | 17 (27.0) |
| | Asian | 22 (35.0) |
| | Black | 13 (20.6) |
| | Mixed/Multiple | 6 (9.5) |
| | Other | 5 (7.9) |
| Marital status | Single/separated/divorced | 56 (88.9) |
| | Married/cohabiting | 7 (11.1) |
| Accommodation | Settled | 58 (92.1) |
| | Not settled | 5 (7.9) |
| Employment status | NEET | 42 (66.7) |
| | In education/training | 12 (19.0) |
| | Employed | 9 (14.3) |
| Education level | Education to 16 only | 46 (73.0) |
| | Education to 18 | 9 (14.3) |
| | Higher education | 8 (12.7) |
| Smoking status | Non smoker | 34 (54.0) |
| | smoker | 29 (46.0) |
| **Clinical variables** | | **N (%) or Median (IQR)** |
| Age at onset of FEP (years) | | 21 (5) |
| Diagnosis | Schizophrenia | 21 (33.3) |
| | Delusional disorder | 2 (3.2) |
| | Schizoaffective disorder | 4 (6.3) |
| | Acute and transient psychosis | 2 (3.2) |
| | Psychosis NOS | 24 (38.1) |
| | Mania with psychosis | 9 (14.3) |
| | Depression with psychosis | 1 (1.6) |

| | | |
|---|---|---|
| DUP (days)† | | 55 (112) |
| DUI (days)‡ | | 270 (619) |
| Psychiatric co-morbidities | Yes | 14 (22.2) |
| | No | 49 (77.8) |
| Psychiatric family history | Yes | 29 (46.0) |
| | No | 34 (54) |
| Number of previous psychiatric hospital admissions (prior to FEP)§ | | 0 (1) |
| Number of previous psychiatric hospital admissions (prior to FEP)¶ | 0 | 41 (65.1) |
| | ≥ 1 | 22 (34.9) |
| History of substance misuse | Yes | 30 (47.6) |
| | No | 33 (52.4) |
| Duration of antipsychotic treatment prior to discontinuation (months) # | | 8.5 (11.3) |
| Type of antipsychotic medication | Oral | 53 (84.1) |
| | Depot | 10 (15.9) |
| Relapse | Yes | 36 (57.0) |
| | Home treatment | 4 (11.1) |
| | Informal hospital admission | 8 (22.2) |
| | Compulsory hospital admission | 11 (30.6) |
| | Clinical team decision | 13 (36.1) |

FEP=first-episode psychosis; Psychosis NOS=psychosis not otherwise specified; DUP=duration of untreated psychosis; DUI=duration of untreated illness; N=number; IQR=inter-quartile range.

**† 2 data missing.**

**‡ 7 data missing.**

**§ c**ontinuous variable.

¶ categorical variable.

**# 1 data missing.**

**Table 2.** Predictors of relapse in univariate and multivariate Cox proportional hazards regression analysis.

| Factors | Univariate model* | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | Exp B (95% CI) | Wald | *P* | Exp B (95% CI) | Wald | *P* |
| **Socio-demographic** | | | | | | |
| **GENDER** | | | | | | |
| Female | 1 | | | | | |
| Male | 3.10 (1.20-8.01) | 5.47 | 0.019** | 3.72 (1.42-9.78) | 7.10 | **0.008**** |
| **ETHNICITY** | | | 0.066 | | | 0.419 |
| White | 1 | | | | | |
| Asian | 0.49 (0.19-1.25) | 1.18 | 0.135 | | | 0.127 |
| Black | 1.75 (0.73-4.22) | 2.25 | 0.214 | NA | | 0.429 |
| Other | 1.71 (0.46-2.97) | 1.56 | 0.740 | | | 0.301 |
| **EMPLOYMENT STATUS** | | | | | | |
| In education/training/employment | 1 | | | 1 | | |
| NEET | 2.55 (1.18-5.48) | 5.70 | 0.017** | 2.24 (1.01-4.97) | 3.94 | **0.047**** |
| **SMOKING STATUS** | | | | | | |
| Non smoker | 1 | | | | | |
| Smoker | 1.89 (0.98-3.68) | 3.56 | 0.059 | NA | | 0.724 |
| **Clinical** | | | | | | |
| No. past psychiatric hospital admissions (1 unit) | 1.96† (1.30-2.96) | 10.41 | 0.001** | 1.94† (1.31-2.88) | 10.94 | **0.001**** |
| **SUBSTANCE MISUSE** | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| No | 1 | | | NA | |
| Yes | 2.22 (1.23-4.35) | 5.35 | 0.002** | | 0.773 |

NEET=not in employment, education or training; NA=not applicable; Exp B=hazard ratio; CI=confidence interval.

† Exp B (hazard ratio) represents relative increase in hazard with one unit increment in variable.

*=predictors with P-value ≤0.1 in univariate analyses were entered in multivariate analysis.

**=significant at 5% level.

**Figure 1.** Kaplan-Meier survival analysis for time to relapse following discontinuation of antipsychotic medication. ⌐, survival function; +, censored. N=63. Cumulative relapse rate = 67%. Median time to relapse = 8 months.

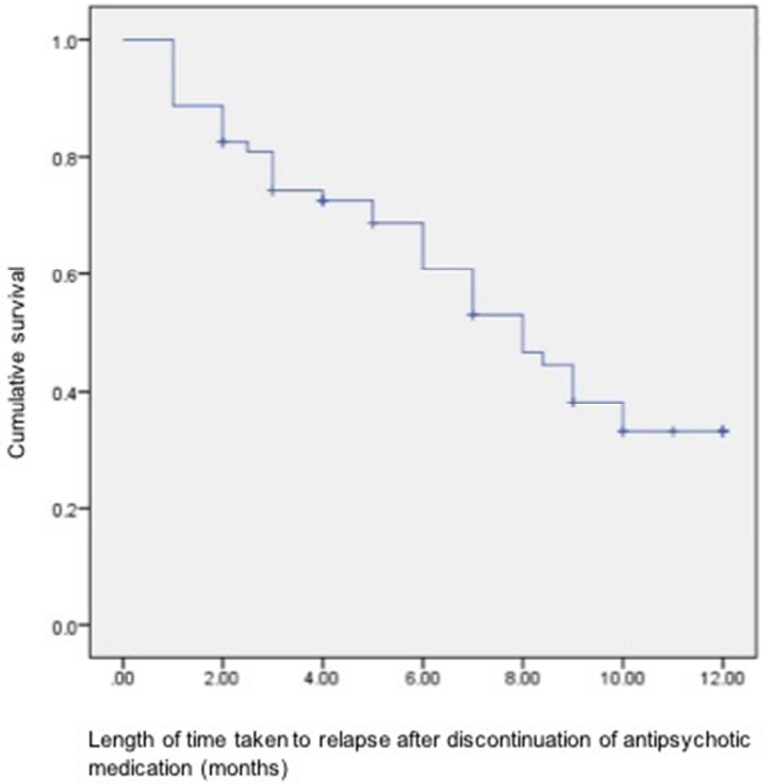


Figure 1: Kaplan-Meier survival analysis for time to relapse following discontinuation of antipsychotic medication. + censored. N=63. Cumulative relapse rate = 67%. Median time to relapse = 8 months.

137x141mm (72 x 72 DPI)